REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested.

The present Amendment is in response to the Office Action mailed August 6, 2009. The present Amendment adds new claims 35-41 and amends claims 1 and 24. Upon entry of the present Amendment claims 1-4, 15, 17-20, 23-26 and 35-41 will be pending.

On pages 3-6 of the Office Action the Examiner rejected claims 1-4, 15, 17-20 and 23-26 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,403,121 (hereinafter Adjei) in view of Menon et al., The American Journal of Gastroenterology, Vol. 96, No. 5, pps. 1631-1634 (2001)(hereinafter "Menon").

Reconsideration is requested.

The present claims currently recite a pharmaceutical dosage form that contains a controlled release metformin core and an immediate release pioglitazone layer surrounding the controlled release core. The dosage form also must release not less than 85% of the pioglitazone within 45 minutes during *in vitro* testing and contain less than 0.6% of the recited pioglitazone impurities. None of the cited references disclose or suggest this unique structure of a controlled release core with only one drug, metformin in the controlled release core and an immediate release layer comprising pioglitazone surrounding the controlled release core, which further provides the recited pioglitazone rapid release and impurity profile.

Claim 1 has been amended to recite that the immediate release pioglitazone component is present in an immediate release layer surrounding the controlled release metformin core. Support for this amendment can be found at least at paragraphs 0037 and Examples 1-6 of U.S. Published Application No. 2006/0161462 (the U.S. publication of the present application).

New claims 35-41 have been added to the present application. These claims are narrower than currently pending claim 1. The impurity profile in these new claims is limited specifically to the five named impurities, and states that each is not present at more than 0.25%. Support for these claims can be found in the specification as originally filed at paragraphs 0018, 0048, 0110-0115, claims 16-18 (as originally filed) and Example 6.

Additionally, claim 24 has been amended to reintroduce the phrase "provides a Tmax of 8-12 hours", which was inadvertently deleted from the claim in the Amendment dated March 31, 2009. No new matter has been added.

The Examiner's primary reference for this rejection is Adjei. The Examiner cites Adjei as disclosing a "core formulation comprising a first layer comprising pioglitazone, which covers at least a portion of a core comprising the biguanide, metformin (i.e. glucophage)". *See* August 6, 2009 Office Action, Page 4.

The Applicants do not dispute that Adjei teaches applying a pioglitazone layer to a metformin core; however, Applicants respectfully submit Adjei does not disclose or suggest a composition comprising a controlled release metformin core surrounded by a separate immediate release pioglitazone layer. Adjei defines "core formulation" as a combination of a metformin core with a pioglitazone coating. For example, Adjei at Col. 1, lines 9-12 states:

> This invention relates to a **core formulation**, and, more particularly, to a **core formulation** comprising a first layer comprising pioglitazone, which covers at least a portion of a **core** comprising the biguanide, metformin (i.e., glucohphage).

(**emphasis** added).

Similarly, Adjei at Col. 2, lines 57-62 states:

> The first layer of the core comprises pioglitazone hydrochloride in an amount of 0.01% to about 20% by weight to the **total weight of the core formulation**, whereas, the metformin in the core is present in an amount of about 10% to 97.5% by weight to the **total weight of the core formulation**.

(**emphasis** added).

See also: Col. 5, lines 29-31 of Adjei (wherein it is stated "The resultant core formulation of the present invention is useful to treat diabetes mellitus") and Claim 1 (which describes the "core formulation" as containing both the biguanide (which may be metformin) and the pioglitazone).

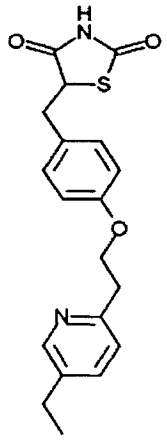
Clearly, Adjei defines the "core formulation" as containing both metformin and pioglitazone. Therefore, when Adjei states the "core formulation of the present invention may be coated with sugar, shellac or other enteric coating agents" (*See* Adjei at Col. 5, lines

63-64), Adjei is instructing the skilled artisan to coat both the metformin and pioglitazone with these coatings. This description is consistent with the teaching on Col. 6, lines 1-7 wherein an embodiment of Adjei is described as the core formulation with the first layer encapsulated by a shell to provide a delayed release of the metformin and pioglitazone. *See also:* Claim 10 of Adjei which describes a method for forming a controlled release dosage form that comprises inserting a metformin and pioglitazone containing core into a shell.

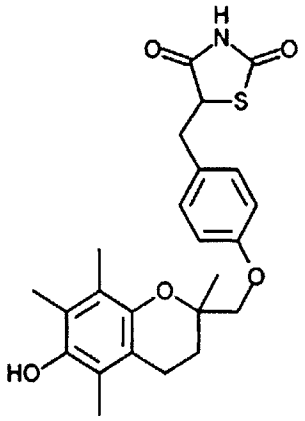
Applicants respectfully submit that Adjei does not disclose a tablet as recited in the present claims because the teachings of Adjei direct a skilled artisan to prepare a "core formulation" comprising both metformin and pioglitazone and applying the modified release coating to the combined "core formulation".

The addition of the Menon article to Adjei does not overcome the deficiencies of Adjei. The Menon article relates to the treatment of patients with troglitazone, which is a different drug from pioglitazone and is not one of the impurities recited in the pending claims. The Examiner states on pages 4-5 of the Office Action that "Menon et al., teaches a pioglitazone related compound or impurity, troglitazone". The International Union of Pure and Applied Chemistry (IUPAC) nomenclature for troglitazone is 5-[[4-[(3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]-phenyl]methyl]-2,4-thiazolidinedione or (±)-5-[4-[(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy]benzyl]-2,4-thiazolidinedione. The IUPAC name for pioglitazone is 5-[[4-[2-(5-ethyl-2pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione; or (±)5-[p-[2-(ethyl-2-pyridyl)ethoxy]benzyl-2,4-thiazolidinedione. *See* The Merck Index (13th Ed. 2001) at pp. 1335 and 1739 (attached hereto as Exhibit A). Neither of the IUPAC names for troglitazone is one of the recited impurities listed in the pending claims.

The structure of pioglitazone and troglitazone are shown below:



Pioglitazone



Troglitazone

As can be seen from a quick review of the images above, the lower portion of the pioglitazone molecule has a pyridine ring, while the troglitazone has a bicyclic two ring structure. These are two different compounds. Applicants further submit that the claimed impurities are also different compounds from the troglitazone molecule. Therefore, Applicants submit that the Menon article has no relevance to the specific pioglitazone impurities recited in the pending claims. While troglitazone is a thiazolidinedione derivative, Applicants submit that a reference discussing side effects related to a different compound does not teach or suggest the desirability to improve the impurity profile by reducing the specifically listed pioglitazone impurities (none of which are troglitazone) as specifically recited in the pending claims. Moreover, Applicants submit new claims 35-41 which are specifically limited to the five recited impurities, none of which recite troglitazone, are not obvious in view of Menon. Additionally, Menon does not provide any teachings with regard to a troglitazone dosage form. It is respectfully submitted that the addition of Menon to Adjei would not provide any guidance to a skilled artisan for modifying the teachings of Adjei to arrive at the presently claimed invention.

On pages 2-3 of the Office Action the Examiner provisionally rejected claims 1-4, 15, 17-20 and 23-26 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 47-50 and 55-63 of co-pending Application No. 11/093,742 (hereinafter the '742 application).

The present application was filed before the '742 application. Further, the '742 application is currently rejected under 35 U.S.C. §§ 103(a). It is respectfully submitted that in view of the above remarks the provisional double patenting rejection will be the only remaining rejection in the present application. The withdrawal of the provisional double patenting rejection is appropriate according to MPEP § 804(I)(B)(1) which reads in relevant part as follows:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier filed application to issue as a patent without a terminal disclaimer.

It is therefore requested that the above double patenting rejection be withdrawn and a notice of allowance issued. Applicants note that a similar provisional double patenting rejection was removed in the present application over co-pending U.S. Application Serial No. 11/094,493 in the Office Action dated February 26, 2009.

Based upon the foregoing amendments and representations, Applicants respectfully request that the rejection of the claims in the above-identified application be withdrawn. Early and favorable action is earnestly solicited.

The Examiner is also invited to telephone the undersigned if any further actions are required to obtain allowance.

Respectfully submitted,

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